IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent Application No. 10/526,697

Applicant: Mark E. DUDLEY et al.

Filed: May 5, 2005

TC/AU: 1644

Examiner: Michail A. Belyavskyi

Docket No.: 233876

Customer No.: 45733

U.S. Patent and Trademark Office
Randolph Building
401 Dulany Street
Alexandria, VA 22314

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Dear Sir:

Applicants request review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a Notice of Appeal.

The review is requested for the reasons stated on the following sheets.

Respectfully submitted,

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Date: 14 May 2009

REASONS FOR PRE-APPEAL BRIEF REQUEST FOR REVIEW

Status of Claims

Claims 1-40 remain pending, wherein claims 23-40 have been rejected, and claims 1-22 have been withdrawn from consideration. The final rejection of claims 23-40 is the subject of this request for review.

Summary of Claimed Subject Matter

In accordance with the embodiment of the invention according to claim 23, the only pending independent claim under examination, a method of promoting the regression of a cancer in a mammal comprises: (i) administering to the mammal nonmyeloablative lymphodepleting chemotherapy, and (ii) subsequently administering: (a) autologous T-cells, which have been previously isolated and selected for highly avid recognition of an antigen of the cancer, the regression of which is to be promoted, by stimulation of the T-cells *in vitro* with the antigen of the cancer, followed by one cycle of rapid expansion using irradiated allogeneic feeder cells, OKT3 antibody, and IL-2, and, either concomitantly with the autologous T-cells or subsequently to the autologous T-cells, by the same route or a different route, a T-cell growth factor that promotes the growth and activation of the autologous T-cells, or (b) autologus T-cells, which have been previously isolated, selected for highly avid recognition of an antigen of the cancer, the regression of which is to be promoted, by stimulation of the T-cells *in vitro* with the antigen of the cancer, and modified to express a T-cell growth factor that promotes the growth and activation of the autologous T-cells, followed by one cycle of rapid expansion using irradiated allogeneic feeder cells, OKT3 antibody, and IL-2, whereupon the regression of the cancer in the mammal is promoted.

As is clear from independent claim 23, the autologous T-cells undergo one cycle of rapid expansion.

Grounds of Rejection to be Reviewed

The grounds of rejection to be reviewed are:

(a) the rejection of claims 23-35, 37 and 38 under § 103 as unpatentable over Dudley et al., *J. Immunotherapy* 24: 363-373 (2001) (hereinafter, "Dudley 2001") or WO '97/05239 (hereinafter, "WO '239") in view of U.S. Patent No. 6,447,767 to Slavin et al. (hereinafter, "Slavin") and Riddell et al., *J. Immunol. Method* 128: 189-201 (1990) (hereinafter, "Riddell"), and U.S. Patent 5,126,132 to Rosenberg (hereinafter, "Rosenberg"); and (b) the rejection of claims 36, 39, and 40 under § 103 as unpatentable over Dudley 2001 or WO '239 in view of Slavin, Rosenberg, and Riddell, as applied to claims 23-35, 37 and 38 above, and further in view of Kawakami et al. *PNAS* 91: 6458-6462 (1994) (hereinafter, "Kawakami") and Stevens et al. *J. Immunol.*, 154: 762-771 (1995) (hereinafter, "Stevens").

Reasons for Withdrawal of Rejection

First, the Office has failed to set forth a *prima facie* case of obviousness. Claim 23 recites administering T cells which have undergone *one* cycle of rapid expansion. The Office Action dated December 17, 2008 states (page 5, 2nd par.) that "[a]ll of the claimed elements were known in the prior art." This is simply incorrect. None of the cited references teach or suggest administering T cells which have undergone *one* cycle of rapid expansion, as claimed. Thus, a *prima facie* case of obviousness has not been made.

Second, even assuming, *arguendo*, that the Office has set forth a prima facie case of obviousness (which it has not), the Office has failed to set forth a valid reason as to why *all of* the rebuttal evidence presented by the Applicants fails to rebut any alleged *prima facie* case of obviousness.

The Office has failed to consider the evidence in the form of the Declaration under 37 C.F.R. § 1.132 by Dr. Mark E. Dudley (hereinafter, "Dudley Declaration") filed on October 17, 2008, Example 1 of the instant application, and studies published in peer-reviewed journals, that the presently claimed method answers a long-felt need in the art to treat patients and succeeds where other methods repeatedly failed. T-cells that undergo *multiple* cycles of rapid expansion provide poor objective clinical results, as evidenced by Dudley 2001, Yee et al., *PNAS,* 99: 16168-73 (2002) (hereinafter, "Yee"), and the Dudley Declaration (¶¶ 5 - 8). In contrast, administering T-cells that have undergone *one* cycle of rapid expansion, as claimed, successfully produces positive objective clinical results in patients, as evidenced by

Example 1 of the instant application, the Dudley Declaration (¶¶ 10-13), and the data published in Dudley et al. *Science* 298: 850-854 (2002) (hereinafter, "Dudley 2002") and Dudley et al., *J. Clin. Oncol.*, 26(32): 5233-5239 (2008) (hereinafter, "Dudley 2008"). The Office has failed to consider the evidence that the presently claimed answers a long-felt need in the art to treat patients and succeeds where other methods have repeatedly failed.

Moreover, the Office has failed to consider the evidence that the presently claimed method provides unexpectedly superior objective clinical responses. As evidenced by the Dudley Declaration (¶¶ 3-9), based on the poor objective clinical results obtained in Dudley 2001 and Yee, one of ordinary skill in the art would *not* have expected that T-cells that had undergone *only one* cycle of rapid expansion, as claimed, would result in a positive, objective clinical response in patients and would logically attempt, instead, to *increase* the number of cycles of rapid expansion. In contrast, the inventors have found that reducing the number of cycles of rapid expansion to *one* cycle, as claimed, successfully produces positive, clinical results, as evidenced by the Dudley Declaration (¶¶ 10-13), the data published in the Dudley 2002 and 2008 references referred to therein, and Example 1 of the instant application. Thus, reducing the number of cycles of expansion to one, as claimed, would be counterintuitive to one of ordinary skill in the art, and illustrates a paradigm shift that is an important contribution over the prior art.

The Office Action has not adequately addressed the applicants' arguments and evidence in support of patentability. MPEP § 2145 explains the legally proper procedure for evaluating obviousness: Assuming, *arguendo*, that a *prima facie* case of obviousness is established (and, as set forth above, the applicants submit it has not been established), the burden shifts to the applicant to come forward with arguments and/or evidence to rebut the *prima facie* case. Rebuttal evidence and arguments can be presented in the specification, by counsel, or by way of an affidavit or declaration under 37 CFR § 1.132. Relevant rebuttal evidence submitted by the applicant *must* be given meaningful consideration. *In re Sullivan*, 84 USPQ2d 1034 (Fed. Cir. 2007); MPEP § 2145. The Office Actions dated December 17, 2008 and March 20, 2009 have not done this.

The counter-arguments by the Office ignore the applicants' arguments and rebuttal evidence in support thereof (in the form of the Dudley Declaration, Example 1 of the

specification, and the Dudley 2002 and 2008 references) that the claimed method, in which the T-cells had undergone *only one* cycle of rapid expansion, provides *unexpectedly superior clinical results* over the methods described in the cited references. The Office Action's comments with respect to arguing references individually, predictability, and motivation to modify or combine references (see, e.g., December 17, 2008 Office Action, page 3, ¶¶ 1-4; page 5, ¶ 2; and page 6, ¶ 2) fail to properly consider this rebuttal evidence. Although the Office Action alleges that the addition of nonmyeloablative lymphodepleting chemotherapy does not provide surprisingly superior results, the Office Action completely fails to consider the fact that reducing the number of cycles of rapid expansion to *one*, as claimed, has produced surprisingly superior, objective clinical results, contrary to the expectations of one of ordinary skill in the art. Thus, an additional issue, which was not addressed by the Office, is that the claimed methods produce unexpectedly superior results. Moreover, the Office Action also fails to consider the evidence that the Applicants have also presented with respect to the expectations of one of ordinary skill in the art, long-felt need, and the repeated failure of other methods in the form of the Dudley Declaration and the Dudley 2001 and Yee references referred to therein, that show that the claimed method successfully treats cancer patients where other methods have repeatedly failed. Because the applicants have clearly rebutted any alleged *prima facie* case of obviousness, the obviousness rejection should be withdrawn.

Since the final rejections of at least the sole pending independent claim are not supportable, the rejections should be withdrawn. Since all of the pending claims are commonly rejected, upon withdrawal of the rejections of claim 23, claims 24-40 should be allowed.

Respectfully submitted,

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